



Efficacy and Tolerability of First-Line Cetuximab Plus Leucovorin, Fluorouracil, and Oxaliplatin (FOLFOX-4) Versus FOLFOX-4 in Patients With *RAS* Wild-Type Metastatic Colorectal Cancer: The Open-Label, Randomized, Phase III TAILOR Trial

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A B S T R A C T

Purpose

Cetuximab in combination with chemotherapy is a standard-of-care first-line treatment regimen for patients with *RAS* wild-type (wt) metastatic colorectal cancer (mCRC); however, the efficacy of cetuximab plus leucovorin, fluorouracil, and oxaliplatin (FOLFOX) has never before been proven in a controlled and randomized phase III trial. To our knowledge, the TAILOR trial (ClinicalTrials.gov identifier: NCT01228734) is the first randomized, multicenter, phase III study of the addition of cetuximab to first-line FOLFOX prospectively choosing a *RAS* wt population and thus providing confirmative data for the efficacy and safety of cetuximab plus FOLFOX versus FOLFOX alone.

Patients and Methods

TAILOR is an open-label, randomized (1:1), multicenter, phase III trial in patients from China comparing FOLFOX-4 with or without cetuximab in *RAS* wt (*KRAS/NRAS*, exons 2 to 4) mCRC. The primary end point of TAILOR was progression-free survival time; secondary end points included overall survival time, overall response rate, and safety and tolerability.

Results

In the modified intent-to-treat population of 393 patients with *RAS* wt mCRC, adding cetuximab to FOLFOX-4 significantly improved the primary end point of progression-free survival time compared with FOLFOX-4 alone (hazard ratio, 0.69; 95% CI, 0.54 to 0.89; $P = .004$; median, 9.2 v 7.4 months, respectively), as well as the secondary end points of overall survival time (current assessment after 300 events: hazard ratio, 0.76; 95% CI, 0.61 to 0.96; $P = .02$; median, 20.7 v 17.8 months, respectively) and overall response rate (odds ratio, 2.41; 95% CI, 1.61 to 3.61; $P < .001$; 61.1% v 39.5%, respectively). Treatment was well tolerated, and there were no new or unexpected safety findings.

Conclusion

The TAILOR study met all of its objectives and relevant clinical end points, confirming cetuximab in combination with FOLFOX as an effective standard-of-care first-line treatment regimen for patients with *RAS* wt mCRC.

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INTRODUCTION

Globally, colorectal cancer is the second most prevalent cancer.^{1,2} Although outcomes in patients with metastatic colorectal cancer (mCRC) have improved over the past decade, the optimal targeted

therapy and backbone first-line chemotherapy for patients with *RAS* wild-type (wt) mCRC remains debated.²

The addition of the anti-epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab to first-line standard infusional fluorouracil (FU)-based chemotherapy improved clinical

ASSOCIATED CONTENT



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outcomes in patients with *RAS* wt mCRC in prior trials.³⁻⁸ The randomized phase III study, Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL), compared the efficacy and safety of first-line cetuximab plus leucovorin, FU, and irinotecan (FOLFIRI) versus FOLFIRI alone; inclusion criteria focused on tumor EGFR expression rather than *KRAS*/*RAS* mutational status.³ Retrospective analysis of patients with *KRAS* exon 2 wt tumors showed that adding cetuximab to FOLFIRI significantly improved progression-free survival (PFS), overall survival (OS), and the overall response rate (ORR).⁴ Additional retrospective analysis of patients with extended *RAS* (*KRAS*/*NRAS*, exons 2 to 4) wt tumors revealed that the addition of cetuximab to FOLFIRI conferred a significant benefit in PFS, OS, and ORR, whereas patients with new *RAS* mutations (outside of *KRAS* exon 2) did not benefit.⁵

Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer (OPUS) was a randomized phase II trial comparing cetuximab plus leucovorin, FU, and oxaliplatin (FOLFOX) versus FOLFOX alone in the first-line treatment of patients with mCRC.⁶⁻⁸ Adding cetuximab to FOLFOX significantly improved the ORR and PFS in patients with *KRAS* exon 2 wt tumors.⁷ Although limited by a small number of patients, retrospective analysis of the population with *RAS* wt tumors suggested a significant ORR benefit from the addition of cetuximab to FOLFOX and numerically increased PFS and OS.⁸ However, this has never been confirmed in a phase III setting.

Controversy persists regarding cetuximab plus FOLFOX combinations based on limited data obtained from the Continuous Chemotherapy Plus Cetuximab or Intermittent Chemotherapy (COIN) and FLOX Plus Cetuximab for Patients With Metastatic Colorectal Cancer and Wild Type K-RAS Tumor (NORDIC VII) trials.^{9,10} However, previous reports have demonstrated that the unexpected lack of efficacy of adding cetuximab to non-FOLFOX, oxaliplatin-containing combinations in COIN and NORDIC VII may be attributable to the use of a nonstandard (noninfusional) bolus or oral fluoropyrimidine-containing chemotherapy regimens in combination with cetuximab rather than any issues with the oxaliplatin plus cetuximab combination.^{11,12} Indeed, the randomized phase III Cancer and Leukemia Group B 80405 study, Cetuximab and/or Bevacizumab Combined With Combination Chemotherapy in Treating Patients With Metastatic Colorectal Cancer, has suggested that cetuximab can be effectively combined with FOLFOX in patients with *RAS* wt mCRC¹³; admittedly, this trial included bevacizumab plus chemotherapy, a comparator arm not available in China at the time the TAILOR trial was initiated. Additional support for cetuximab plus FOLFOX is provided by the Cetuximab in Neoadjuvant Treatment of Non-Resectable Colorectal Liver Metastases (CELIM), Study Evaluating the Safety and Efficacy of FOLFIRI Plus Cetuximab or FOLFOX Plus Cetuximab as First-Line Therapy in Subjects With *KRAS* Wild-type Metastatic Colorectal Cancer (APEC)¹⁴⁻¹⁶; randomized phase III trials investigating the consequences of adding cetuximab to FOLFOX are lacking.

The scientific evidence for extended *RAS* testing (*v* solely *KRAS* exon 2 testing) accumulated after prior trials completed enrollment. Therefore, a potential limitation of those studies is that their analyses of patients with *RAS* wt tumors were performed retrospectively. The TAILOR trial was designed to address this limitation, as well as provide definitive phase III verification regarding the utility of cetuximab in combination with first-line FOLFOX, by serving, to

our knowledge, as the first prospective, randomized, phase III study to confirm the efficacy and safety of adding cetuximab to first-line FOLFOX in patients with *RAS* wt mCRC. FOLFOX was selected as the chemotherapy backbone for the TAILOR trial because it is the preferred first-line chemotherapy regimen in Asia.¹⁷

PATIENTS AND METHODS

Patients and Study Design

TAILOR (Trial No.: EMR62202-057; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01228734) identifier: NCT01228734) was an open-label, randomized, multicenter, phase III trial comparing cetuximab plus FOLFOX-4 versus FOLFOX-4 alone in the first-line treatment of patients with mCRC. With the target of 247 events for the primary end point, the study would have 80% power to detect differences between the two treatment arms ($\alpha = .05$; two sided), anticipating a median PFS time of 10 months in the cetuximab plus FOLFOX-4 arm and 7 months in FOLFOX-4 arm. Follow-up time was calculated from the random assignment date to the date the patient was last known to be alive. For patients who died, follow-up time was censored on the date of death.

Patients were randomly assigned 1:1 to receive either cetuximab plus FOLFOX-4 or FOLFOX-4 according to an unstratified block randomization. This was an open-label study. A blinded review of imaging and clinical data for the primary end point of PFS time and the secondary end point of ORR was carried out by an independent review committee (IRC).

At trial initiation (September 2010), patients with *KRAS* exon 2 wt tumors were enrolled. As a result of scientific evidence external to the study,^{5,8,18} inclusion was later changed to patients with extended *RAS* (*KRAS*/*NRAS* exons 2 to 4) wt tumors, and the analysis was based on this modified intent-to-treat (mITT) population; there was no requirement for detectable tumor EGFR expression. The cutoff date for the main analysis was in January 2016.

The trial was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committees of all participating centers. All patients gave written informed consent before trial entry.

Outcomes

The primary efficacy analysis population was composed of all patients with *RAS* wt tumors who received any dose of trial treatment (ie, the *RAS* wt mITT population). PFS time, as assessed by an IRC according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, was the primary end point of TAILOR. PFS time was defined as the time from random assignment until first observation of radiologically confirmed progressive disease or death as a result of any cause within 90 days of the last tumor assessment or random assignment (whichever was later).

Secondary end points included OS, ORR, and safety and tolerability. PFS and ORR assessments were performed according to RECIST version 1.0 and were undertaken separately by the investigators and an IRC; the blinded IRC review of imaging data was used for the primary statistical analysis. Investigator assessments served as the basis for on-study decisions (ie, treatment continuation or discontinuation) and were considered in sensitivity analyses. The National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 was used for recording adverse events (AEs). AEs were coded according to the Medical Dictionary for Regulatory Activities and graded using the National Cancer Institute Common Terminology Criteria toxicity grades. Details regarding eligibility, procedures, subgroup analyses, and statistics are in the Data Supplement.

RESULTS

Patient Populations

A total of 1,425 patients were prescreened for tumor *KRAS*/*RAS* status. Of the 553 patients with *KRAS* exon 2 wt tumors, 504

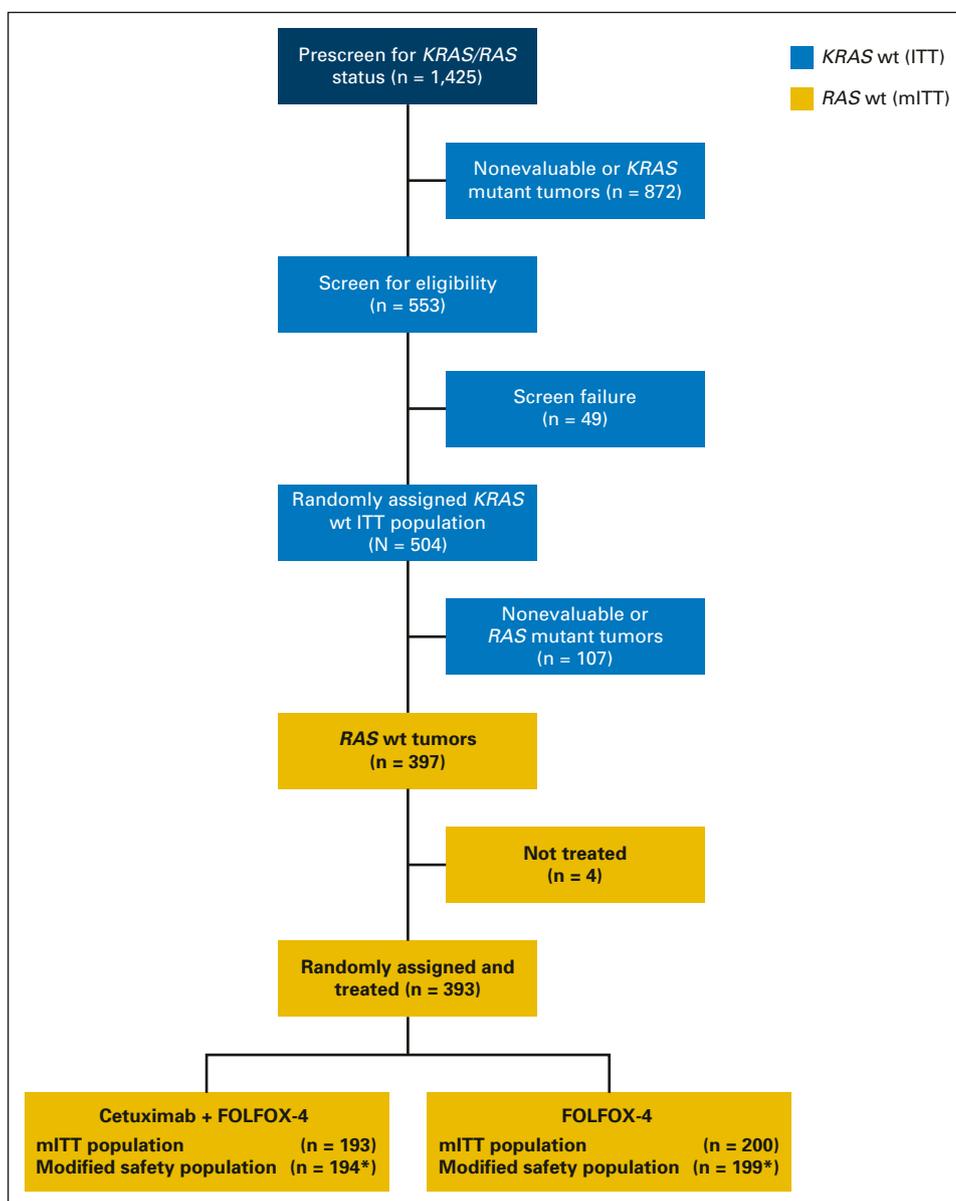


Fig 1. TAILOR study patient disposition. (*) One patient randomly assigned to the leucovorin, fluorouracil, and oxaliplatin (FOLFOX-4) arm received cetuximab plus FOLFOX-4; this patient was included in the FOLFOX-4 arm of the mITT population considered for efficacy analysis but the cetuximab plus FOLFOX-4 arm of the modified safety population considered for safety analysis. ITT, intent to treat; mITT, modified intent to treat; wt, wild type.

were deemed eligible. After amendment of the inclusion criteria to include only patients with fully RAS (*KRAS/NRAS* exons 2 to 4) wt mCRC, 107 patients with RAS-mutant or RAS-nonevaluable tumors were screened out. Of the 397 patients with RAS wt tumors who were randomly assigned, 393 were treated. The mITT population was composed of these 393 patients with RAS wt mCRC (Fig 1). One patient randomly assigned to the FOLFOX-4 arm received cetuximab plus FOLFOX-4 and was included in the FOLFOX-4 arm of the mITT population for efficacy analyses but the cetuximab plus FOLFOX-4 arm of the modified safety population for safety analyses.

Baseline characteristics were reasonably balanced between treatment arms in patients with RAS wt tumors (Table 1). Median follow-up in patients with RAS wt tumors was 44.4 and 48.7 months in the cetuximab plus FOLFOX-4 and FOLFOX-4 arms, respectively.

Cumulative dose, number of courses, and relative dose-intensity data from the population of patients with RAS wt tumors are presented in the Data Supplement and confirm balanced treatment

exposure between arms. Briefly, the median duration of treatment with cetuximab was 32.0 weeks (range, 1.0 to 209.0 weeks). The median duration of oxaliplatin treatment was 25.8 weeks (range, 2.0 to 128.0 weeks) in the cetuximab plus FOLFOX-4 arm and 21.0 weeks (range, 2.0 to 64.0 weeks) in the FOLFOX-4 arm.

Efficacy

In the population of patients with RAS wt tumors, adding cetuximab to FOLFOX-4 significantly improved the primary end point of PFS time by IRC (hazard ratio [HR], 0.69; 95% CI, 0.54 to 0.89; $P = .004$; median, 9.2 months with FOLFOX-4 plus cetuximab v 7.4 months with FOLFOX-4 alone; Fig 2A). In a sensitivity analysis, counting all deaths as events (v only deaths within 90 days of the last tumor assessment or random assignment, as in the primary end point definition) yielded consistent PFS time results (HR, 0.56; 95% CI, 0.45 to 0.70; $P < .001$; median, 8.7 v 5.6 months with FOLFOX-4

Table 1. Baseline Characteristics in the *RAS* Wild-Type Modified Intent-to-Treat Population

Characteristic	No. of Patients (%)	
	Cetuximab + FOLFOX-4 (n = 193)	FOLFOX-4 (n = 200)
Sex		
Male	127 (65.8)	139 (69.5)
Female	66 (34.2)	61 (30.5)
Age, years		
Median	56.0	56.0
Range	21-83	21-78
ECOG performance status		
0	63 (32.6)	66 (33.0)
1	130 (67.4)	134 (67.0)
No. of metastatic disease sites		
1	72 (37.3)	80 (40.0)
2	81 (42.0)	63 (31.5)
3	27 (14.0)	36 (18.0)
> 3	13 (6.7)	21 (10.5)
Liver metastasis only		
No	141 (73.1)	144 (72.0)
Yes	52 (26.9)	56 (28.0)
Alkaline phosphatase, U/L		
< 300	175 (90.7)	186 (93.0)
≥ 300	15 (7.8)	11 (5.5)
Missing	3 (1.6)	3 (1.5)
Leukocytes		
≤ 10,000/mm ³	174 (90.2)	186 (93.0)
> 10,000/mm ³	19 (9.8)	14 (7.0)
EGFR-positive cells, %		
0	85 (44.0)	77 (38.5)
> 0-10	35 (18.1)	48 (24.0)
> 10-20	15 (7.8)	14 (7.0)
> 20-35	9 (4.7)	14 (7.0)
> 35	29 (15.0)	28 (14.0)
Missing	20 (10.4)	19 (9.5)
<i>BRAF</i> status		
Mutant	27 (14.0)	25 (12.5)
Wild type	166 (86.0)	175 (87.5)
LDH		
≤ ULN	96 (49.7)	103 (51.5)
> ULN	85 (44.0)	76 (38.0)
Missing	12 (6.2)	21 (10.5)
Primary tumor location		
Both colon and rectum	1 (0.5)	0
Colon and rectum combined	1 (0.5)	0
Colon only	93 (48.2)	105 (52.5)
Appendix	2 (1.0)	2 (1.0)
Ascending colon	20 (10.4)	16 (8.0)
Cecum	2 (1.0)	8 (4.0)
Descending colon	8 (4.1)	13 (6.5)
Hepatic flexure	8 (4.1)	5 (2.5)
Sigmoid colon	39 (20.2)	52 (26.0)
Splenic flexure	1 (0.5)	3 (1.5)
Transverse colon	13 (6.7)	9 (4.5)
Rectum only	98 (50.8)	95 (47.5)
Rectosigmoid junction	8 (4.1)	2 (1.0)
Rectum	90 (46.6)	93 (46.5)
Missing	1 (0.5)	0
Prior chemotherapy		
Total for all indications	52 (26.9)	54 (27.0)
Any adjuvant chemotherapy	51 (26.4)	50 (25.0)
With oxaliplatin	43 (22.3)	41 (20.5)
Without oxaliplatin	8 (4.1)	9 (4.5)
Neoadjuvant chemotherapy	0	2 (1.0)
For metastatic disease*	1 (0.5)	2 (1.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; FOLFOX-4, leucovorin, fluorouracil, and oxaliplatin; LDH, lactate dehydrogenase; ULN, upper limit of normal.

*Regarded as a protocol violation.

plus cetuximab *v* FOLFOX-4 alone, respectively). Furthermore, comparable PFS time results were obtained from a sensitivity analysis in which disease progression was assessed by the investigator (*v* IRC; HR, 0.65; 95% CI, 0.51 to 0.82; *P* < .001; median, 9.2 *v* 7.4 months with FOLFOX-4 plus cetuximab *v* FOLFOX-4 alone, respectively).

After 300 events (76.3% of the population of patients with *RAS* wt tumors), assessment of OS time at cutoff for the primary end point of PFS also showed clinically relevant and statistically significant benefit from the addition of cetuximab to FOLFOX-4 (HR, 0.76; 95% CI, 0.61 to 0.96; *P* = .02; median, 20.7 *v* 17.8 months with FOLFOX-4 plus cetuximab *v* FOLFOX-4 alone, respectively; Fig 2B). Relatively few patients received additional therapy after progression (42.5% and 46.0% of patients in the cetuximab plus FOLFOX-4 and FOLFOX-4 arms, respectively, received second-line anticancer chemotherapy treatment), and only 15% of patients in the FOLFOX-4 arm compared with 1.6% of patients in the cetuximab plus FOLFOX-4 arm received later-line EGFR-targeting therapies.

The secondary end point of confirmed ORR was also significantly improved with the addition of cetuximab to FOLFOX-4 according to the IRC review (odds ratio [OR], 2.41; 95% CI, 1.61 to 3.61; *P* < .001; 61.1% *v* 39.5% with FOLFOX-4 plus cetuximab *v* FOLFOX-4 alone, respectively). Similar to the PFS time results, investigator-assessed ORR was also highly comparable to the IRC results in a sensitivity analysis (OR, 2.89; 95% CI, 1.92 to 4.36; *P* < .001; 66.3% *v* 40.5% with FOLFOX-4 plus cetuximab *v* FOLFOX-4 alone, respectively). Finally, eight patients in the cetuximab plus FOLFOX-4 arm and six patients in the FOLFOX-4 arm underwent surgery with curative intent; seven and two patients in the cetuximab plus FOLFOX-4 and FOLFOX-4 arms, respectively, had R0 resections.

As shown in Figure 3, efficacy in the cetuximab plus FOLFOX-4 arm was consistently higher in nearly all subgroups, except for *BRAF*-mutant patients. However, the suggested negative treatment effect may be subject to some uncertainty as a result of the small subgroup of patients with *BRAF*-mutated tumors and an imbalance in baseline characteristics in this subgroup. Notably, treatment activity was independent of tumor EGFR expression status. Data for all other subgroups should also be interpreted with caution as a result of low patient numbers.

Considering recent evidence regarding the potential prognostic and predictive value of primary tumor location,²⁰⁻²² we also examined its effect on outcomes in the population of patients with *RAS* wt tumors via a post hoc hypothesis-generating exploratory subgroup analysis. Baseline characteristics were reasonably balanced between treatment arms in the left-sided tumor location subgroup; however, among patients with right-sided tumors, there were multiple imbalances between treatment arms (data not shown). Nevertheless, the prognostic effect of primary tumor location (right *v* left sided) within the treatment arms could be shown for PFS (HR, 1.72; 95% CI, 1.16 to 2.55; *P* = .007), OS (HR, 1.84; 95% CI, 1.25 to 2.70; *P* = .002), and ORR (OR, 0.40; 95% CI, 0.20 to 0.80; *P* = .014) in the cetuximab plus FOLFOX-4 arm, as well as for PFS (HR, 1.97; 95% CI, 1.28 to 3.02; *P* = .002), OS (HR, 1.43; 95% CI, 0.97 to 2.10; *P* = .073), and ORR (OR, 0.41; 95% CI, 0.18 to 0.92; *P* = .028) in the FOLFOX-4 arm. A sensitivity analysis excluding tumors originating from the

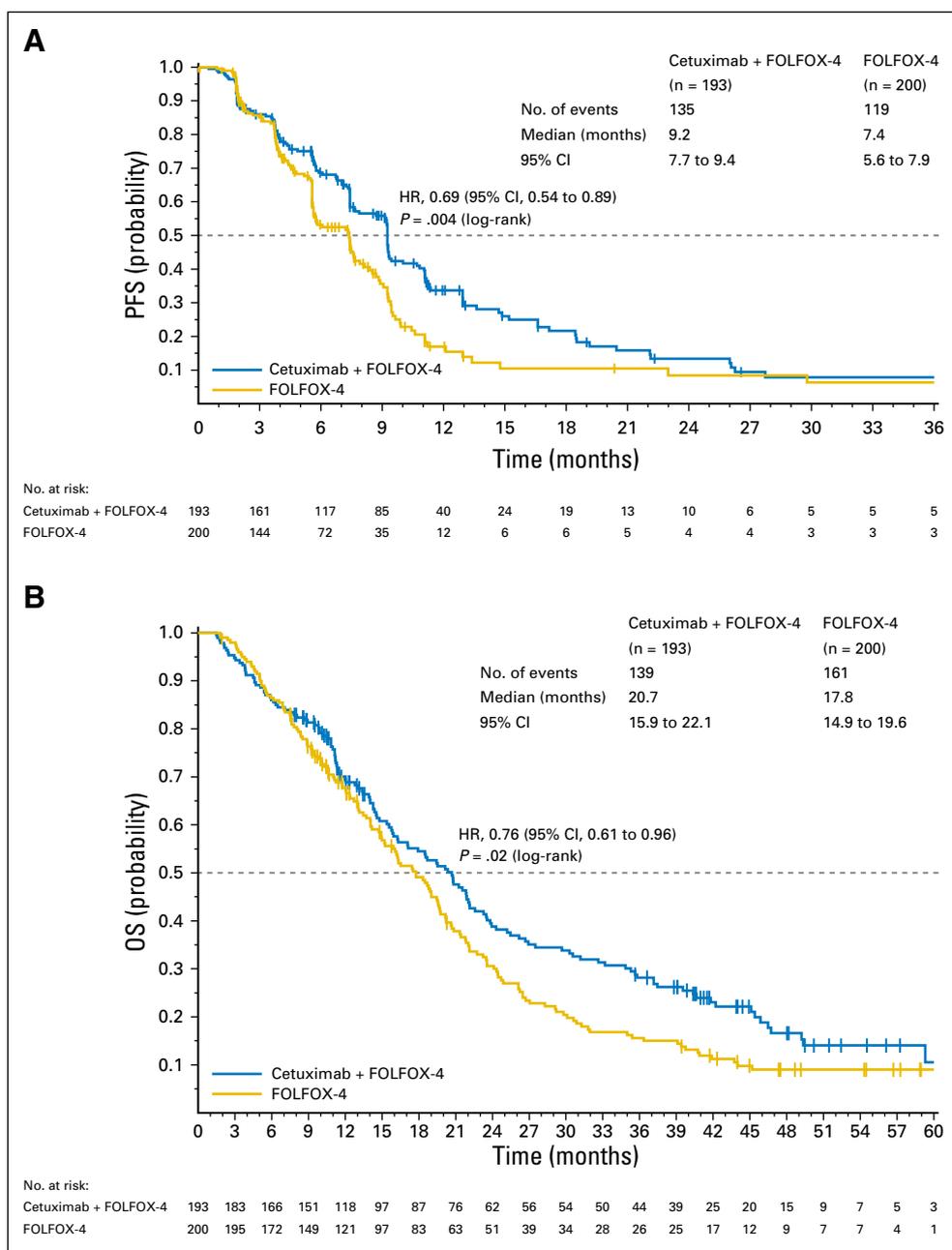


Fig 2. (A) Primary end point of progression-free survival (PFS) time by independent review committee in the RAS wild-type modified intent-to-treat population. (B) Secondary end point of overall survival (OS) time in the RAS wild-type modified intent-to-treat population. FOLFOX-4, leucovorin, fluorouracil, and oxaliplatin; HR, hazard ratio.

transverse colon did not alter the conclusions (data not shown). The efficacy of cetuximab plus FOLFOX-4 versus FOLFOX-4 alone by primary tumor location is summarized in Table 2. In a multivariable analysis that included treatment, sex, tumor location, prior adjuvant therapy, and BRAF status, the P values for the interaction between primary tumor location and treatment were P = .4575 (PFS), P = .0839 (OS), and P = .9154 (ORR); thus, a potential predictive effect of primary tumor location was not confirmed.

Safety

The incidence of treatment-emergent AEs in the population with RAS wt tumors was in line with expectations^{5,8} (Table 3).

Neutropenia was the most common grade ≥ 3 treatment-emergent AE in both treatment arms (the incidence of grade ≥ 3 febrile neutropenia was 1% in both arms). Grade ≥ 3 skin reactions occurred in 25.8% of patients in the cetuximab plus FOLFOX-4 arm (23.7% acne-like rash). Serious AEs were experienced by 19.1% of patients who received cetuximab plus FOLFOX-4 compared with 13.1% of patients treated with FOLFOX-4 (5.7% and 5.5% of patients had treatment-related serious AEs, respectively). In the cetuximab plus FOLFOX-4 arm, 16.0% of patients discontinued cetuximab as a result of an AE. AEs caused discontinuation of chemotherapy in 39.2% and 27.1% of patients in the cetuximab plus FOLFOX-4 and FOLFOX-4 arms, respectively. There were eight AEs leading to death in the cetuximab plus FOLFOX-4 arm and five AEs leading to death in the FOLFOX-4 arm; however,

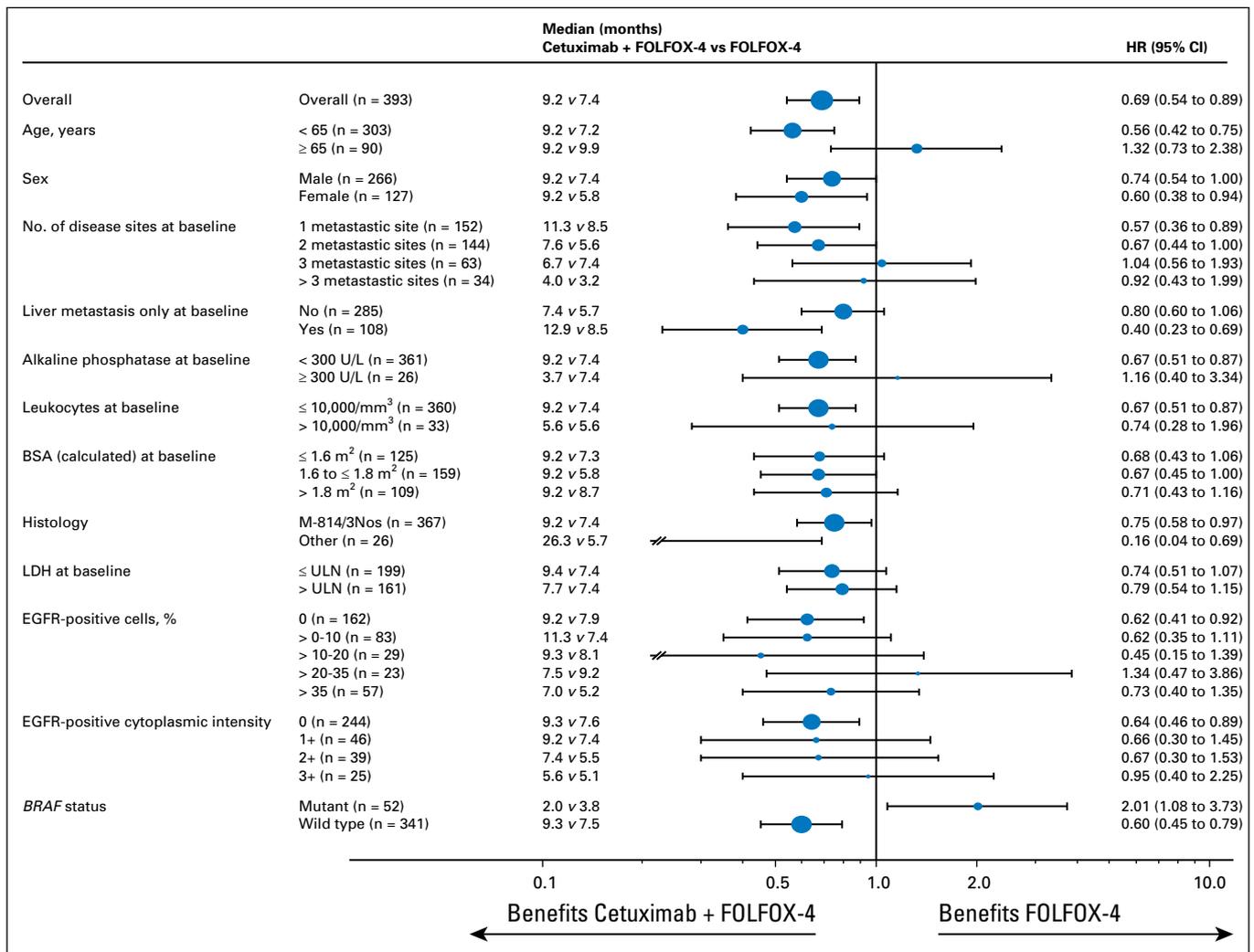


Fig 3. Forest plot of demographic- and biomarker-defined subgroup analyses involving the primary end point of progression-free survival time by independent review committee in the *RAS* wild-type modified intent-to-treat population. BSA, body surface area; EGFR, epidermal growth factor receptor; FOLFOX-4, leucovorin, fluorouracil, and oxaliplatin; HR, hazard ratio; LDH, lactate dehydrogenase; M-184/3Nos, adenocarcinoma, not otherwise specified; ULN, upper limit of normal.

this includes AEs of all potential causes (not necessarily drug related), and there were no deaths specifically related to cetuximab.

DISCUSSION

To our knowledge, TAILOR is the first prospective, parallel-group, multicenter, randomized, phase III trial to study the efficacy and safety of adding cetuximab to first-line FOLFOX in patients with *RAS* wt mCRC independent of EGFR status. We report that adding cetuximab to FOLFOX-4 significantly improved PFS, OS, and ORR in patients from China with *RAS* wt mCRC. Chemotherapy exposure was less than that in historical trials but similar between treatment arms; relative dose-intensity was comparable to that in prior reports.^{5,8} Higher cumulative chemotherapy doses in the cetuximab plus FOLFOX-4 arm versus the FOLFOX-4 alone arm likely reflect longer treatment durations, which are attributable to longer PFS time in the cetuximab plus FOLFOX-4 arm. Therefore, our observations are consistent with prior, retrospective, phase II data from the randomized OPUS study.^{5,8} Moreover, there were no

new or unexpected safety findings; the safety profile of cetuximab plus FOLFOX was similar to that observed in prior randomized clinical trials.⁸ Thus, the TAILOR study provides robust evidence for clinical practice regarding cetuximab in combination with FOLFOX as a standard-of-care first-line treatment for patients with *RAS* wt mCRC. This unequivocally settles the academic question surrounding the cetuximab plus FOLFOX combination that has been disputed in past years.^{9,10}

There were no major differences between our observations and those previously reported from analogous pivotal trials in mCRC that enrolled predominantly white patients.^{5,8} Although the absolute incidence of neutropenia and leukopenia in the FOLFOX-4 arm of this population of patients from China was higher than is generally seen in global trials, the relative increase in incidence in the cetuximab plus FOLFOX-4 arm was consistent with that in other trials⁸; furthermore, the incidence of grade ≥ 3 febrile neutropenia was 1% in both treatment arms in the TAILOR study. Similarly, there was a meaningful number of infusion-related reactions in the FOLFOX-4 arm of the TAILOR trial, but the relative increase in incidence upon adding cetuximab was in line

Table 2. Effect of Primary Tumor Location on Efficacy in the RAS Wild-Type mITT Population

Population and Treatment Arm	No. of Patients	PFS (primary end point)			OS			ORR		%
		HR (95% CI)	P for HR (log-rank test)	Median (months)	HR (95% CI)	P for HR (log-rank test)	Median (months)	OR (95% CI)	P for OR (Fisher's exact test)	
mITT*		0.69 (0.54 to 0.89)	.004		0.76 (0.61 to 0.96)	.020		2.41 (1.61 to 3.61)	< .001	
Cetuximab + FOLFOX-4	193			9.2			20.7			61.1
FOLFOX-4	200			7.4			17.8			39.5
Left sided		0.68 (0.50 to 0.91)	.009		0.69 (0.53 to 0.90)	.006		2.60 (1.64 to 4.14)	< .001	
Cetuximab + FOLFOX-4	146			9.2			22.0			66.4
FOLFOX-4	162			7.6			18.7			43.2
Right sided (transverse colon included)		0.67 (0.40 to 1.11)	.117		0.94 (0.58 to 1.51)	.787		2.58 (1.00 to 6.67)	.065	
Cetuximab + FOLFOX-4	45			7.4			11.3			44.4
FOLFOX-4	38			4.5			9.3			23.7
Right sided (transverse colon excluded)		0.77 (0.42 to 1.39)	.377		0.99 (0.56 to 1.76)	.975		2.44 (0.81 to 7.35)	.177	
Cetuximab + FOLFOX-4	32			7.4			11.3			43.8
FOLFOX-4	29			4.5			9.5			24.1

Abbreviations: FOLFOX-4, leucovorin, fluorouracil, and oxaliplatin; HR, hazard ratio; mITT, modified intent to treat; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
*Two patients in the cetuximab plus FOLFOX-4 arm were not evaluable for tumor location.

with previous observations.⁸ Finally, we acknowledge that the median OS time observed in TAILOR is lower than that reported in other contemporary trials^{5,13,19}; however, this is likely attributable to the fact that relatively few patients in TAILOR received additional therapy after progressing on the first-line regimen (< 50% of patients in TAILOR received second-line anticancer chemotherapy treatment compared with, for example, > 75% of patients in FOLFIRI Plus Cetuximab Versus FOLFIRI Plus Bevacizumab in

First Line Treatment Colorectal Cancer [FIRE-3]¹⁹), including limited access to targeted agents in subsequent lines of therapy. Overall, optimizing the treatment sequence by including biologics in the second and third therapy lines in China could potentially improve survival outcomes in patients with RAS wt mCRC; investigations of the effects of treatment sequencing are ongoing.

Our observations suggest that adding cetuximab to FOLFOX-4 seems to benefit patients regardless of whether their tumors express

Table 3. Most Common Grade ≥ 3 Treatment-Emergent Adverse Events in the RAS Wild-Type Modified Safety Population (> 5% incidence in either treatment arm)

Adverse Event	No. of Patients (%)			
	Cetuximab + FOLFOX-4 (n = 194)		FOLFOX-4 (n = 199)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
MedDRA preferred term				
Neutropenia	155 (79.9)	120 (61.9)	149 (74.9)	86 (43.2)
Leukopenia	151 (77.8)	52 (26.8)	146 (73.4)	42 (21.1)
Rash	118 (60.8)	27 (13.9)	6 (3.0)	0
Fatigue	75 (38.7)	25 (12.9)	52 (26.1)	19 (9.5)
Hypokalemia	61 (31.4)	20 (10.3)	37 (18.6)	8 (4.0)
Thrombocytopenia	90 (46.4)	20 (10.3)	100 (50.3)	13 (6.5)
Hypomagnesemia	35 (18.0)	16 (8.2)	5 (2.5)	2 (1.0)
Dermatitis acneiform	31 (16.0)	14 (7.2)	1 (0.5)	0
Stomatitis	32 (16.5)	12 (6.2)	14 (7.0)	1 (0.5)
Diarrhea	70 (36.1)	11 (5.7)	33 (16.6)	4 (2.0)
Bone marrow failure	17 (8.8)	9 (4.6)	13 (6.5)	12 (6.0)
Composite categories				
Skin reactions				
Any	158 (81.4)	50 (25.8)	16 (8.0)	0
Acne-like rash	156 (80.4)	46 (23.7)	16 (8.0)	0
Infusion-related reaction	95 (49.0)	19 (9.8)	73 (36.7)	12 (6.0)

Abbreviations: FOLFOX-4, leucovorin, fluorouracil, and oxaliplatin; MedDRA, Medical Dictionary for Regulatory Activities.

EGFR, consistent with prior reports^{14,23-25} as well as the current European Society for Medical Oncology and National Comprehensive Cancer Network guidelines.^{2,26}

In the small subgroup of patients with *BRAF* mutations, a negative treatment effect is suggested, which is not in line with other reports,²⁷⁻²⁹ where some benefit was described with the addition of cetuximab to chemotherapy or best supportive care in patients with *BRAF*-mutant mCRC. Contradictory conclusions were also drawn from two meta-analyses investigating the effects of anti-EGFR monoclonal antibodies in *BRAF*-mutant mCRC.^{30,31} Whereas Rowland et al³¹ concluded that there is insufficient evidence to justify the exclusion of anti-EGFR therapy for patients with *RAS* wt/*BRAF*-mutant mCRC, Pietrantonio et al³⁰ discouraged the use of these therapies in these patients. The adverse finding in the TAILOR trial might be related to nonbalanced baseline characteristics in this subgroup. However, it was clearly shown that patients with *BRAF* wt tumors derive a higher treatment benefit than patients with *BRAF*-mutated tumors, as suggested by current European Society for Medical Oncology and National Comprehensive Cancer Network guidelines,^{2,26} in which doublet chemotherapies with a biologic are no longer recommended for this subgroup. Current recommendations for patients with *BRAF*-mutant tumors include rather toxic triplet chemotherapy, but as suggested by the Southwest Oncology Group (SWOG) 1406 trial ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT02164916)³² and currently being investigated in the Study of Encorafenib + Cetuximab Plus or Minus Binimetinib v Irinotecan/Cetuximab or Infusional 5-Fluorouracil (5-FU)/Folinic Acid (FA)/Irinotecan (FOLFIRI)/Cetuximab With a Safety Lead-in of Encorafenib + Binimetinib + Cetuximab in Patients With *BRAF* V600E-mutant Metastatic Colorectal Cancer (BEACON) trial ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT02928224),³³ combinations including cetuximab and a *BRAF* inhibitor might be the future for this currently underserved population. In addition, the FIRE-4.5 study (European Union Clinical Trials Register: AIO KKK-0116) is investigating first-line cetuximab plus FOLFOX and irinotecan versus bevacizumab plus FOLFOX and irinotecan in patients with *BRAF*-mutant mCRC.

Furthermore, via a post hoc hypothesis-generating exploratory subgroup analysis, we report that adding cetuximab to first-line FOLFOX-4 seemed to benefit patients compared with FOLFOX-4 alone, regardless of primary tumor location in terms of PFS, OS, and ORR. We did not detect any interaction between primary tumor location and treatment. Indeed, patients with right-sided, *BRAF* wt mCRC seemed to benefit from the addition of

cetuximab to FOLFOX-4, even though the patient numbers are small (Data Supplement). Therefore, the present observations are partly in contrast to previously presented subgroup results from the first-line cetuximab CRYSTAL, FIRE-3, and Cancer and Leukemia Group B 80405 trials,^{21,22} although our findings in patients with left-sided tumors are consistent with a recently reported meta-analysis that considered both cetuximab and panitumumab trials.³⁴ Furthermore, the observed ORR with cetuximab in right-sided mCRC in the TAILOR trial is consistent with previous observations and provides additional support for the continuing role for cetuximab in this patient population when cytoreduction is a key treatment goal.

In conclusion, the TAILOR trial is, to our knowledge, the first randomized phase III study of the addition of cetuximab to first-line FOLFOX prospectively choosing a *RAS* wt population and thus providing confirmative data for the efficacy and safety of cetuximab plus FOLFOX versus FOLFOX in *RAS* wt mCRC, independent of EGFR status. Accordingly, the benefit-to-risk ratio for first-line cetuximab plus FOLFOX remains positive.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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REFERENCES

- Parkin DM, Bray F, Ferlay J, et al: Global cancer statistics, 2002. *CA Cancer J Clin* 55:74-108, 2005
- Van Cutsem E, Cervantes A, Adam R, et al: ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 27:1386-1422, 2016
- Van Cutsem E, Köhne CH, Hitre E, et al: Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 360:1408-1417, 2009
- Van Cutsem E, Köhne CH, Láng I, et al: Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: Updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* 29:2011-2019, 2011
- Van Cutsem E, Lenz HJ, Köhne CH, et al: Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. *J Clin Oncol* 33:692-700, 2015
- Bokemeyer C, Bondarenko I, Makhson A, et al: Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 27:663-671, 2009
- Bokemeyer C, Bondarenko I, Hartmann JT, et al: Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: The OPUS study. *Ann Oncol* 22:1535-1546, 2011
- Bokemeyer C, Köhne CH, Ciardiello F, et al: FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer. *Eur J Cancer* 51:1243-1252, 2015
- Maughan TS, Adams RA, Smith CG, et al: Addition of cetuximab to oxaliplatin-based first-line

combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 377:2103-2114, 2011

10. Tveit KM, Guren T, Glimelius B, et al: Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: The NORDIC-VII study. *J Clin Oncol* 30:1755-1762, 2012

11. Vale CL, Tierney JF, Fisher D, et al: Does anti-EGFR therapy improve outcome in advanced colorectal cancer? A systematic review and meta-analysis. *Cancer Treat Rev* 38:618-625, 2012

12. Taieb J, Maughan T, Bokemeyer C, et al: Cetuximab combined with infusional 5-fluorouracil/folinic acid (5-FU/FA) and oxaliplatin in metastatic colorectal cancer (mCRC): A pooled analysis of COIN and OPUS study data. *J Clin Oncol* 30, 2012 (suppl; abstr 3574)

13. Lenz H, Niedzwiecki D, Innocenti F, et al: CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with expanded RAS analyses in untreated metastatic adenocarcinoma of the colon or rectum (mCRC). *Ann Oncol* 25, 2014 (suppl 4; abstr 5010)

14. Chang AL, Cornelio GH, Shen L, et al: Final analysis of the phase 2 APEC study: Overall survival (OS) data and biomarker subanalyses for first-line FOLFIRI or FOLFIRI with cetuximab (cet) once every 2 weeks in patients (pts) with KRAS or RAS (KRAS and NRAS, exons 2-4) wild-type (wt) metastatic colorectal cancer (mCRC). *J Clin Oncol* 33, 2015 (suppl 3; abstr 566)

15. Folprecht G, Gruenberger T, Bechstein WO, et al: Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: The CELIM randomised phase 2 trial. *Lancet Oncol* 11:38-47, 2010

16. Ocvirk J, Brodowicz T, Wrba F, et al: Cetuximab plus FOLFOX6 or FOLFIRI in metastatic colorectal cancer: CECOG trial. *World J Gastroenterol* 16:3133-3143, 2010

17. Cheng AL, Li J, Vaid AK, et al: Adaptation of international guidelines for metastatic colorectal cancer:

An Asian consensus. *Clin Colorectal Cancer* 13:145-155, 2014

18. Douillard JY, Oliner KS, Siena S, et al: Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med* 369:1023-1034, 2013

19. Heinemann V, von Weikersthal LF, Decker T, et al: FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): A randomised, open-label, phase 3 trial. *Lancet Oncol* 15:1065-1075, 2014

20. Brulé SY, Jonker DJ, Karapetis CS, et al: Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. *Eur J Cancer* 51:1405-1414, 2015

21. Venook AP, Neidzwiecki D, Innocenti F, et al: Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). *J Clin Oncol* 34, 2016 (suppl; abstr 3504)

22. Tejpar S, Stintzing S, Ciardiello F, et al: Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: Retrospective analyses of the CRYSTAL and FIRE-3 trials. *JAMA Oncol* 10.1001/jamaoncol.2016.3797 [Epub ahead of print on October 10, 2016]

23. Chung KY, Shia J, Kemeny NE, et al: Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. *J Clin Oncol* 23:1803-1810, 2005

24. Cunningham D, Humblet Y, Siena S, et al: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 351:337-345, 2004

25. Hebbard M, Wacrenier A, Desauw C, et al: Lack of usefulness of epidermal growth factor receptor expression determination for cetuximab therapy in patients with colorectal cancer. *Anticancer Drugs* 17:855-857, 2006

26. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. V2.2016. https://www.nccn.org/professionals/physician_gls/default.aspx

27. Bokemeyer C, Van Cutsem E, Rougier P, et al: Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials. *Eur J Cancer* 48:1466-1475, 2012

28. Karapetis CS, Jonker D, Daneshmand M, et al: PIK3CA, BRAF, and PTEN status and benefit from cetuximab in the treatment of advanced colorectal cancer: Results from NCIC CTG/AGITG CO.17. *Clin Cancer Res* 20:744-753, 2014

29. Stintzing S, Miller-Phillips L, Modest DP, et al: Impact of BRAF and RAS mutations on first-line efficacy of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab: Analysis of the FIRE-3 (AIO KRK-0306) study. *Eur J Cancer* 79:50-60, 2017

30. Pietrantonio F, Petrelli F, Coiu A, et al: Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: A meta-analysis. *Eur J Cancer* 51:587-594, 2015

31. Rowland A, Dias MM, Wiese MD, et al: Meta-analysis of BRAF mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for RAS wild-type metastatic colorectal cancer. *Br J Cancer* 112:1888-1894, 2015

32. Kopetz S, McDonough SL, Lenz H-J, et al: Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406). *J Clin Oncol* 35, 2017 (suppl; abstr 3505)

33. Huijberts S, Schellens JHM, Fakih M, et al: BEACON CRC (binimetinib [BINI], encorafenib [ENCO], and cetuximab [CTX] combined to treat BRAF-mutant metastatic colorectal cancer [mCRC]): A multicenter, randomized, open-label, three-arm phase III study of ENCO plus CTX plus or minus BINI vs irinotecan (IRI)/CTX or infusional 5-fluorouracil/folinic acid (IFL)/CTX with a safety lead-in of ENCO + BINI + CTX in patients (pts) with BRAFV600E mCRC. *J Clin Oncol* 35, 2017 (suppl; abstr TPS3622)

34. Holch JW, Ricard I, Stintzing S, et al: The relevance of primary tumour location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials. *Eur J Cancer* 70:87-98, 2017

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